UNIVERSITÉ DE GENÈVE

PRESS RELEASE

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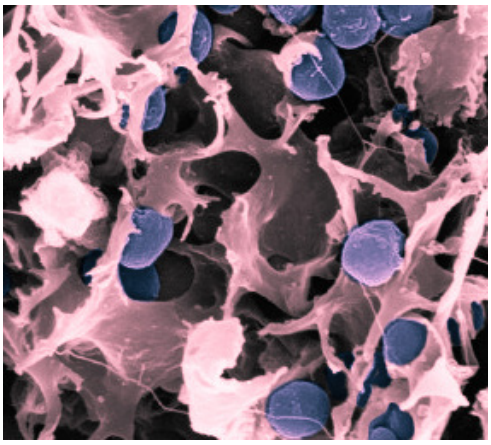
A Protein for Strengthening Thymic Activity

In the University of Geneva (UNIGE) Faculty of Medicine's Pathology and Immunology Department, researchers are emphasizing the catalytic role that the CYR61 protein plays in the thymus—headquarters of immune cell development. The experiments involving this protein led to an appreciable increase in the production of these cells, the T lymphocytes. The results of this research are the subject of an article in the latest edition of the journal *Nature Communications*.

The thymus is a strange organ. It is discreetly housed at the bottom of the throat, and its swollen shape is characteristic of a dish loved by foodies: veal sweetbreads. Beat Imhof, professor in the UNIGE Faculty of Medicine's Pathology and Immunology Department, smilingly said that its role is equivalent to an "immune cell school". A school of hard knocks, as the thymus is where the T lymphocytes are trained to kill pathogens.



Microscopical view into a thymus: purple cells are on the way of becoming T lymphocytes while pink cells are epithelial cells forming cavities to «train» the purple ones. Photo: DR

A protein that stimulates cell proliferation

In Professor Imhof's laboratory, researcher Yalin Emre noticed that the CYR61 protein, known in scientific literature to promote cell proliferation (including cancer cells), is expressed by epithelial cells in the thymus. In other words, the thymus produces the CYR61 protein. What connection does the protein have with its neighbors inside the organ? Yalin Emre's research has highlighted its affinities with the T lymphocytes and the thymic stroma cells, on to which it attaches.

A positive effect on thymic cells

Research continued on tissue culture, then *in vivo* on mice, confirming the protein's two roles: promoting the proliferation of thymic epithelial cells, and fostering their contact with immature T lymphocytes developing in the thymus.

Finally, with the intent to utilize the CYR61's capacity in a healthy environment, researchers administered the protein to thymi in vitro. Those organs developed significantly. Their stromal cells proliferated, inflating the volume of the thymi. The same result was observed in vivo, on thymi treated with the protein, and which had been transplanted on mice without thymi. The capacity of transplanted organs to recruit hematopoietic stem cells increased, and consequently, the production of developing T lymphocytes increased as well. The quantity of forming immune cells doubled compared to those produced by a non-stimulated thymus. However, the phenomenon occurred in a very proportional way, because in both the stroma and the lymphocytes, the individual development capacity of cells that came into contact with the CYR61 protein remained identical to that of cells present in a natural thymus.

From immature cells to T lymphocytes, expert killers

These observations open up interesting prospects for strengthening the thymus, which plays a key role in our immunity. In fact, after passing

through this organ, the hematopoietic stem cells born in our bone marrow are transformed into T lymphocytes, i.e. they are equipped with an *ad hoc* receiver that will help each one of them recognize only one type of molecule to hunt down. If, among these molecules, there are some that are part of our own body—"the self"—the thymus is tasked with deactivating the developing T lymphocytes susceptible of killing the self. In wartime, during an infection, it's a race against time between the production of immune cells and pathogens, which multiply and seek to take control of our cells in order to reproduce at full speed.

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A key organ in the fight against infections, the thymus works in two steps: first, it produces enormous amounts of so-called "immature" cells; then, among these immature cells, the thymus delegates to its stroma cells—its own constitutive cells—the responsibility of selecting the ones capable of distinguishing the "non-self", so that once they are released into the bloodstream, they can efficiently attack each of their corresponding pathogens.

Age, strengths, and weaknesses of the thymus

But with age, and immediately after puberty, the thymus diminishes then shrivels. Yet it remains active throughout the entire life of a human being—a life that tends to be increasingly long in rich countries. With the aging of the population, it is advantageous for industrialized societies to look into ways of preventing infections that prey on weaker organisms, such as the chronically ill and the elderly. With certain genetic diseases, the blood cells that form in bone marrow—the famous hematopoietic stem cells—are unable to distinguish the T lymphocytes, even after their trip through the thymus. Strengthening the thymus and curbing its natural degeneration could therefore help offset some deficiencies.

Therapeutic possibilities

In cultivation, CYR61's catalytic strength was only observed on the epithelial cells of the thymic stroma. *In vivo*, transplants of thymus lobes treated with the protein increased the organ's volume and caused a noticeable increase of T lymphocytes in the blood of immunodeficient mice. The treated and transplanted thymus functioned normally, i.e. its cells did not exhibit anarchic development. Such findings portend promising possibilities regarding therapeutic research aimed at countering thymic obsolescence.

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